

### **REMARKS/ARGUMENTS**

Upon entry of this amendment, claims 1-13, 15-17, 19-21, 23-54, 57-61, 65, 68-72, and 74 are pending in this application and are presented for examination. Claims 1-13, 15-17, 19-21, 23-51, 53, 65 and 68-71 have been allowed. Claims 14, 18, 22, 55-56, 62-64, 66-67, and 73 have been canceled without prejudice. Claims 52, 54, 57-60, 69-70, and 72 have been amended. No new matter has been introduced with the foregoing amendments. Reconsideration is respectfully requested.

#### **I. FORMALITIES**

The specification has been amended to correct typographical errors with respect to the "Poynard et al." reference. These are obvious errors that a skilled person would readily recognize as such. Thus, no new matter has been introduced. Applicants respectfully request that the amendments to the specification be entered.

Claims 57-60 and 69-70 have been amended to establish proper claim dependency. Support for amended claims 52, 54, and 72 is found throughout the specification as filed. In particular, support for amended claim 52 is found, for example, from page 39, line 27 to page 41, line 27. Support for amended claim 54 is found, for example, from page 43, line 9 to page 44, line 2, in the paragraph bridging pages 44-45, and in Table 8 on page 104. Support for amended claim 72 is found, for example, on page 32, lines 9 to 29, in the paragraph bridging pages 34-35, and in Example II on pages 95-103. Thus, no new matter has been introduced. As such, Applicants respectfully request that the amendments to the claims be entered.

#### **II. REJECTION UNDER 35 U.S.C. § 112, SECOND PARAGRAPH**

Claims 52, 72, and 74 were rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as their invention. To the extent the rejection is applicable to the amended set of claims, Applicants respectfully traverse the rejection.

The Examiner alleges that claim 52 is confusing because it states nothing about the "individual" in relation to the "population" recited. In order to expedite prosecution of the present case, Applicants have amended claim 52 to recite that in a population having up to 30% liver fibrosis prevalence, X1, Y1, Z1, X2, Y2, and Z2 are independently selected to differentiate F0-F1 fibrosis from F2-F4 fibrosis *in the individual* with a positive predictive value of at least 90% or a negative predictive value of at least 90% in at least 65% of the population assayed.

The Examiner also alleges that claim 72 is confusing because it does not indicate which of the cut-off values is higher for a specific fibrotic marker. In response, Applicants have amended claim 72 to recite that the cut-off values X2, Y2, and Z2 are *greater than or equal to* X1, Y1, and Z1, respectively.

Further, the Examiner alleges that claim 72 is incomplete for omitting the steps employed in a dual optimization strategy as set forth in Example II. In order to expedite prosecution, Applicants have amended claim 72 to recite a method for diagnosing the presence or severity of liver fibrosis by first comparing a level of the fibrotic markers  $\alpha$ 2-MG, HA, and TIMP-1 to a first set of cut-off values and further evaluating an individual positive for all three markers by comparing the level of the markers to a second set of cut-off values.

In view of the above amendments to the claims, Applicants respectfully request that the Examiner withdraw all the 35 U.S.C. § 112, second paragraph rejections.

### **III. REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH**

Claims 54-63 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled the art that Applicants, at the time the application was filed, had possession of the claimed invention. To the extent the rejection is applicable to the amended set of claims, Applicants respectfully traverse the rejection.

The Examiner alleges that claim 54 contains new matter by reciting "up to 60% liver fibrosis prevalence" and "at least about 70% accuracy." In order to expedite prosecution, Applicants have amended claim 54 to recite the use of the fibrotic markers  $\alpha$ 2-MG, HA, and TIMP-1, wherein in a population having *about 40%* liver fibrosis prevalence, the cut-off value

for each marker is independently selected to diagnose the presence or severity of liver fibrosis in the individual with **more than 91%** accuracy in **about 70%** of the population assayed.

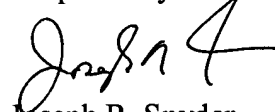
Applicants submit that the instant specification contains adequate written description of the percentages recited in amended claim 54 (*see, e.g.*, the paragraph bridging pages 44-45). In particular, the instant specification describes that in a patient population with **about 40%** liver fibrosis prevalence, **almost 70%** of the population is diagnosed with **more than 91%** accuracy (*see*, page 44, lines 27-30). Further, the instant specification discloses that the claimed method provides an improvement over the method of Imbert-Bismut et al. because a significantly greater percentage of the patient population, *i.e.*, **about 70%** as compared to about 50%, are diagnosed with an accuracy of **more than 91%** as compared to about 89% (*see*, page 45, lines 9-14). As a result, Applicants assert that the percentages recited in amended claim 54 are adequately disclosed in the instant specification. In view of the foregoing, Applicants respectfully request that the Examiner withdraw the 35 U.S.C. § 112, first paragraph rejection.

### CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 925-472-5000.

Respectfully submitted,



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